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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,074	05/07/2007	James M. Cregg	67858.701501	9018

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EXAMINER

VOGEL, NANCY TREPTOW

ART UNIT	PAPER NUMBER
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1636

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01/05/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/577,074	Applicant(s) CREGG ET AL.	
	Examiner NANCY VOGEL	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 September 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/18/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 22-58 are pending in the case.

Receipt of the Information Disclosure Statement on 12/10/09 is acknowledged.

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection that were not necessitated by applicants' amendment and therefore, this action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained essentially for the reasons made of record in the previous Office action, mailed 3/18/09 (previously addressed to claim 21). Applicant's arguments have been considered but have not been found convincing.

Response to Amendment

The Declaration under 37 CFR 1.132 filed 9/18/09 is sufficient to overcome the rejection of claims 41-44 based upon 35 USC 112 p.1.

The Declaration under 37 CFR 1.132 filed 132 is insufficient to overcome the rejection of claims 41-44 (formerly claim 21 was rejected) based upon 35 USC 112 p.1 as set forth in the last Office action because:

The Declaration is addressed to evidence that an antibody (heavy chain and light chain) can be produced at levels recited in the claims using the claimed method. However, the claims are not limited to methods of producing antibodies in *Pichia*, but rather recite broadly any heteromultimeric polypeptide. Therefore the Declaration is not commensurate in scope with the claims. There is unpredictability in the ability of *Pichia* to be capable of producing any particular polypeptide, as stated in the specification at page 2 last paragraph. Therefore, the rejection is maintained.

The following are new rejections necessitated by applicant's amendments:

Claim Objections

Claims 46 is objected to because of the following informalities:

Claim 46 recites "are maintain" which is grammatically incorrect.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed. Newly submitted claim 22 (and dependent claims) is of broader scope than original claim 1, since it discloses that the method for synthesis and recovery of a secreted, biologically active heterologous heteromultimeric polypeptide comprises producing a diploid *Pichia* cells by mating or spheroplast fusion of haploid *Pichia* cells, wherein the diploid cells comprise at least one expression construct which encode for at least two non-identical subunit polypeptide chains. However, the original claims and the originally filed specification only provide support for mating two haploid cells, wherein each haploid cell comprises one expression vector, each of which encodes one subunit of a heteromultimeric protein, for a total of two subunits. Furthermore, claims 36-44 and 48-55 now recite such terms as “at least 50 g/L”, “at least 50 mg/L”, “at least 99%”, etc. However, the specification only recites those numbers with the modifying word “about” (see p. 64, 66-70). There is no support for the claims as instantly amended. This a new matter rejection. The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned limitations, as currently

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recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 36-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of production of antibodies in diploid *Pichia* cells, does not reasonably provide enablement for the recited cell densities, levels of heteromultimeric polypeptide produced, or high levels of expression after 20, 30, or 100 doublings, or levels of 99% of diploid cells comprising expression constructs after at least 20, 50, 100 doublings, or levels of heteromultimeric polypeptides produced which are not reduced by more than 20% after 20, 50 or 100 doublings, or levels of expression which are not reduced by more than 10%, or 5% relative to the starting level of expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed

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Nature of the invention: The nature of the invention is a method of polyploid Pichia culture capable of stably expressing a heteromultimeric polypeptide for a prolonged doubling times, for high levels of expression..

Breadth of the claims: The claims are broad because they encompass methods for producing high levels of polypeptide, over long periods of time, at high cell density, and without loss of expression vector or expression levels.

Guidance of the specification: The only examples have colonies growing for 2-3 days. There are no examples of yeast cultures stably expressing and secreting heterologous peptides for a prolonged period of time, including at least 100 doublings. There are not examples of high levels of expression which are stable over time, and high densities of cells. There are not examples of high levels of expression.

While there is mention of yeast cultures being able to stably express and secrete heterologous peptides for a prolonged period of time, there is no explanation as to why or how they are able to. There are no examples of yeast cultures being able to stably express and secrete heterologous peptides for a prolonged period of time.

Amount of experimentation necessary: The amount of experimentation would be undue because Applicants do not give any guidance as to what gives a yeast culture the ability to stably express and secrete heterologous peptides for a prolonged period of time. It is unclear if the yeast are mutated, or if the yeast are expressing a particular protein with characteristics that allow for prolonged expression and secretion, for example. It is also unknown if this applies only to Pichia, or to other yeast. The

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experimentation is undue because Applicants do not teach how to make and use these yeast cultures. While the Declaration discussed above provides examples of producing high levels of antibodies in *Pichia*, it is not commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-58 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 and by dependence claims 23-58 are vague and indefinite in the recitation of "heterologous (non-yeast)" for the following reasons:

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte*

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Hasche, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation “heterologous”, and the claim also recites “non-yeast” which is the narrower statement of the range/limitation.

Claims 29 and 30 lack antecedent basis for “the first or second promoters” in the claim on which they depend (claim 22) since said claim does not recite first or second promoters.

Claim 31 lacks antecedent basis for “the diploid yeast cells” since the claim on which it depends (claim 22) does not recite “yeast cells”.

Claim 32 lacks antecedent basis for “said production media” since the claim on which it depends (claim 30) does not recite “production media”.

Claims 33 and 34 lack antecedent basis for “said minimal media” since the claim on which it depends (claim 31) does not recite “minimal media”.

Claim 35 is vague and indefinite in the recitation of “a high cell density” since it is not clear what metes and bounds of the claimed subject matter are intended. “High” is a relative term which is not defined.

Claims 45-47 are vague and indefinite in the recitation of “high levels of expression” since it is not clear what is intended. The metes and bounds of what is encompassed by “high levels” are not defined.

Claim 54 and 55 are vague and indefinite, since they recite the method of claim 31 in which expression is reduced by not more than 5% or 10% relative to the starting level of expression. However, it is not clear at what point the expression level is measured, and therefore the intended metes and bounds are unclear.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
12/31/09